

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : C07B 63/00, C07C 231/24, 237/46		A1	(11) International Publication Number: <b>WO 99/18054</b> (43) International Publication Date: 15 April 1999 (15.04.99)
(21) International Application Number: PCT/GB98/02955 (22) International Filing Date: 2 October 1998 (02.10.98) (30) Priority Data: 9720969.6 2 October 1997 (02.10.97) GB (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/069,925 (CIP) Filed on 17 December 1997 (17.12.97) (71) Applicant (for all designated States except US): NYCOMED IMAGING AS [NO/NO]; Nycoveien 1-2, N-0401 Oslo (NO). (71) Applicant (for GB only): SKAILES, Humphrey, John [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): CERVENKA, Jan [NO/NO]; Nycomed Imaging AS, Nycoveien 1-2, N-0401 Oslo (NO).		(74) Agents: SKAILES, Humphrey, John et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: PROCESS FOR THE CRYSTALLISATION OF STERICALLY HINDERED COMPOUNDS (57) Abstract <p>A process for the crystallisation of a sterically hindered organic compound from a saturated or supersaturated solution of said compound in a solvent therefor, characterised in that crystallisation is effected under elevated pressure at a temperature above the boiling point of said solution at atmospheric pressure up to the boiling point of said solution at said elevated pressure.</p>			

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## PROCESS FOR THE CRYSTALLISATION OF STERICALLY HINDERED COMPOUNDS

This invention relates to a process for the crystallization from solution of a chemical species having multiple conformations with steric hindrance to transitions between such conformations.

The vast majority of organic compounds are capable of adopting different conformations, generally as a result of rotations about sigma bonds. Where the compounds contain bulky groups however there is significant steric hindrance to such rotations and as a result transitions between stable (or metastable) conformations occur relatively slowly.

For crystallization of a substance to occur, the substance must adopt the conformation required by the crystalline structure. Accordingly, crystallization of sterically hindered compounds can take place relatively slowly. A high degree of supersaturation is normally required for acceleration of crystallization, resulting in limited purity in the crystalline product.

This is the case for example with the iodophenyl compounds commonly used as X-ray contrast agents and is particularly true for the so-called dimeric compounds which contain two iodophenyl groups per molecule, e.g. compounds such as iodixanol and iotrolan, which may take days to crystalize.

As a result, the manufacture of such compounds is extremely demanding in terms of time and equipment.

We have now found that crystallization of such sterically hindered compounds from solution may be accelerated, and/or the need for a high degree of supersaturation may be reduced, by crystallization with high thermal energy. The necessary thermal energy can be achieved by use of a boiling solvent (or boiling solvent mixture) or crystallization under pressure.

Crystallization under pressure is performed at

- 2 -

temperatures above the boiling point (at atmospheric pressure) of the solution.

The invention thus provides a time-saving method and/or a method which will improve the purity of the product.

Thus viewed from one aspect the invention provides a process for the crystallization of a sterically hindered organic compound from a saturated or more preferably supersaturated solution of said compound in a solvent therefor, characterised in that crystallization is effected with high thermal energy.

One preferred aspect of the invention provides a process for the crystallization of a sterically hindered organic compound from a saturated or more preferably supersaturated solution of said compound in a solvent therefor, characterised in that crystallization is effected under elevated pressure at a temperature above the boiling point of said solution at atmospheric pressure (ie. ambient pressure, e.g. 1 bar) and up to the boiling point of said solution at said elevated pressure.

The necessary thermal energy may also be achieved by crystallization at the boiling point of the solvent or solvent mixture at atmospheric conditions. Under such working conditions the thermal energy input is limited by the boiling point of the solvent or solvent mixture used.

Thus a further preferred aspect of the invention provides a process for the crystallization of a sterically hindered organic compound from a saturated or more preferably supersaturated solution of said compound in a solvent therefor, characterised in that crystallization is effected at the boiling point of the solvent or solvent mixture used.

In the processes of the invention, the supersaturated solution may for example be produced from a non-saturated solution (e.g. by evaporation of a

- 3 -

solvent or by cooling), or by dissolving amorphous material at elevated temperatures, or by the addition of a material (e.g. an anti-solvent) which reduces the solubility in the solvent system of the substance to be crystallized.

Crystallization from the supersaturated solution may be started by the use of a crystallization initiator, e.g. seed crystals of the sterically hindered compound. These may be added to the supersaturated solution before, during or after temperature and pressure are raised.

The solvent used in the processes of the invention may be a single solvent or a solvent mixture. Any solvent or solvent mixture capable of forming a liquid solution of the sterically hindered compound may be used although solvents such as water, alcohols, ketones, esters, ethers, and hydrocarbons are preferred, especially water, alcohols, alcohol-ethers, ethers and ketones, e.g.  $C_{1-4}$  alcohols.

Examples of suitable solvents include water, methanol, ethanol, n-propanol, isopropanol, n-butanol, i-butanol, sec-butanol, t-butanol, pentanols including isoamyl alcohol, methoxyethanol, ethylene glycol, propylene glycol, acetone, ethyl-methyl ketone, formaldehyde, acetaldehyde, dimethyl ether, diethylether, methylethyl-ether, tetrahydrofuran, ethylacetate, methyl cyanide, dimethylsulphoxide, dimethylformamide, benzene, toluene, xylene, n-hexane, cyclohexane, n-heptane, etc.

Especially preferably, the solvent comprises one or more  $C_{1-6}$  alkanols, alkoxyalkanols, linear or cyclic ethers, optionally together with a minor quantity (e.g. up to 10 wt %) of water.

Especially preferably, the solvent or solvent mixture used is a low-boiling or moderate boiling point material, e.g. having a boiling point of  $-10$  to  $+100^{\circ}\text{C}$  at ambient pressure, especially  $30$  to  $80^{\circ}\text{C}$ , particularly

- 4 -

40 to 70°C. The solvent or solvent mixture however should be stable at the temperature and pressure conditions used. It is also preferred that the crystallization be effected at a temperature below 200°C, especially below 150°C and most preferably below 120°C, and for crystallization under pressure that this be a temperature at least 10° particularly at least 15°C above the boiling point of the solution under ambient pressure.

An added advantage of the pressure crystallization aspect of the invention is that the solubility of the sterically hindered compound is higher at the temperatures used than at temperatures below the boiling point of the solution at ambient pressure. As a result, the quantity of solvent used can be reduced as can the volume of the crystallizer vessel. Moreover solvents in which the sterically hindered compound is only relatively poorly soluble under ambient conditions may be usable and as a result it may be feasible to use more environmentally friendly solvent systems for crystallization (or recrystallization).

The sterically hindered compound crystallized according to the processes of the invention will preferably be a compound having at ambient temperature in solution (e.g. in water, C<sub>1-4</sub> alcohol or C<sub>1-4</sub> ether) at least two stable conformations with an activation energy at ambient conditions of at least 50 kJ/mole, preferably at least 80 kJ/mole, and preferably no more than 200 kJ/mole, for transition between these conformations. This activation energy may be calculated by standard techniques of quantum chemistry, etc.

In general, the processes of the invention are suitable for compounds which have a high activation energy for crystal growth, e.g. higher than 50 kJ/mole.

Examples of suitable compounds include hydroxyalkyl and/or acylamino and/or alkylaminocarbonyl derivatives of 2,4,6-triiodophenyl monomers and dimers such as those

- 5 -

proposed or used as X-ray contrast agents (and in particular the non-ionic agents), for example diatrizoate, iobenzamate, iocarmate, iocetamate, iodamide, iodipamide, iodixanol, iohexol, iopentol, ioversol, iopamidol, iotrolan, iodoxamate, ioglicate, ioglycamate, iomeprol, iopanoate, iophenylate, iopromide, iopronate, ioserate, iosimide, iotasul, iothalamate, iotroxate, ioxaglate, ioxitalamate, metrizamide and metrizoate, as well as the monomers and dimers of WO96/09285 and WO96/09282.

Besides such iodinated x-ray contrast agents, the processes of the invention are also applicable to crystallization of other sterically hindered compounds, in particular pharmaceutical compounds, especially substances having highly restricted side chain rotations or other conformational changes. Such substances should of course be crystallized at temperatures at which they are stable. The processes moreover are applicable to all substances with low solubility in a selected low-boiling solvent regardless of the activation energy of the steric changes.

The pressure applied in the pressure crystallization aspect of the invention will conveniently be such as to ensure that the boiling point of the saturated or supersaturated solution is raised relative to the boiling point at ambient pressure by at least 10°C, especially at least 15°C and more especially at least 20°C. The maximum pressure will generally be dictated by design constraints on the apparatus used but in general an overpressure of 0.05 to 20 bar, particularly 0.2 to 10 bar, especially 1.5 to 6 bar may be used.

The crystallization should therefore be performed in a vessel capable of withstanding the temperature and pressure conditions used. In general a stainless steel batch or continuous reactor equipped for stirring, heating and provided with means for applying and

- 6 -

releasing pressure may be used.

In the "boiling point" aspect of the invention the choice of solvent will reflect not only the capability to form a liquid mixture, but also the need for thermal energy in order to achieve an effective crystallization process. The process is especially suitable for the crystallization of iodixanol with the solvent being methanol or a mixture of methanol (0-100% by volume), propan-2-ol (0-80% by volume) and water (0-10% by volume).

The invention will now be described with reference to the following non-limiting Examples:

#### Example 1

80g of solid iodixanol containing 3% wt water was dissolved in 374 mL methanol under reflux under ambient pressure. 48 mL of propan-2-ol were added and the solution was seeded with 1.6g of iodixanol crystals. The mixture was maintained under reflux and the crystallization was followed by monitoring the iodixanol content of the mother liquor. When this had stabilized after 24 hours, the crystalline iodixanol was removed. Yield: 89% (24 hours)

#### Example 2

An iodixanol solution prepared and seeded as in Example 1 was placed in an autoclave and stirred for 5 hours at 90°C under an overpressure of about 2 bar. The autoclave was cooled and the crystalline iodixanol recovered. Yield: 91%

- 7 -

Example 3

150g of dry raw iohexol has been dissolved in 50 ml 2-methoxyethanol in an autoclave. 1.5g iohexol seeds were added and the solution heated up to 100°C. A solubility gradient was created by a controlled addition of 150 ml 2-propanol (b.p. 82.4°C) during a 5-hour period at constant temperature 100°C, followed by a controlled cooling to 70° in 3 hours. After additional 3 hours equilibration, the crystals were filtered off and washed by 2-methoxyethanol/2-propanol and finally dried.

Yield: 90%

Purity: 99.1%

A reference experiment ran under reflux provided a purity of 98.6%.

Claims

1. A process for the crystallization of a sterically hindered organic compound from a saturated or more preferably supersaturated solution of said compound in a solvent therefor, characterised in that crystallization is effected with high thermal energy.
2. A process as claimed in claim 1, characterised in that crystallization is effected under elevated pressure at a temperature above the boiling point of said solution at atmospheric pressure and up to the boiling point of said solution at said elevated pressure.
3. A process as claimed in claim 1, characterised in that crystallization is effected at the boiling point of the solvent or solvent mixture used.
4. A process as claimed in any preceding claim wherein said sterically hindered compound is a triiodophenyl group containing compound.
5. A process as claimed in any preceding claim wherein said solvent has a boiling point at atmospheric pressure (1 bar) of -10 to +100°C.
6. A process as claimed in claim 2 wherein said elevated pressure is an overpressure of from 0.05 to 20 bar.
7. A process as claimed in claim 2 wherein crystallization is effected at a temperature at least 10°C above the boiling point of the solution at atmospheric pressure (1 bar).
8. A process as claimed in claim 3 wherein said compound is iodixanol and said solvent is methanol or a

- 9 -

mixture of methanol (0-100% by volume), propan-2-ol  
(0-80% by volume) and water (0-10% by volume).

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02955

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07B63/00 C07C231/24 C07C237/46

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07B C07C B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 747 344 A (HOVIONE INTER) 11 December 1996 see examples	1,3-5
X	US 4 250 113 A (V. NORDAL) 10 February 1981 see example 2	1,4
X	GB 2 280 436 A (ZAMBON GROUP) 1 February 1995 see examples	1,3-5
X	DE 44 25 340 A (CIBA-GEIGY) 1 December 1994 see page 4, line 42 - line 45; example 1	1,3
A	EP 0 108 638 A (NYEGAARD) 16 May 1984 see example 3	1,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 November 1998

Date of mailing of the international search report

03/12/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Wright, M

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 98/02955

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 747344 A	11-12-1996	PT 101720 A	31-01-1997
		AT 162180 T	15-01-1998
		AU 695662 B	20-08-1998
		AU 5451296 A	19-12-1996
		CA 2178369 A	09-12-1996
		CZ 9601632 A	11-12-1996
		DE 69600144 D	19-02-1998
		DE 69600144 T	20-05-1998
		ES 2114336 T	16-05-1998
		JP 8333319 A	17-12-1996
US 4250113 A	10-02-1981	GB 1548594 A	18-07-1979
		BE 855580 A	12-12-1977
		CH 630064 A	28-05-1982
		DE 2726196 A	22-12-1977
		DK 258477 A,B,	12-12-1977
		FR 2354316 A	06-01-1978
		HK 56683 A	25-11-1983
		JP 1113258 C	16-09-1982
		JP 53021137 A	27-02-1978
		JP 56054310 B	24-12-1981
		NL 7706385 A,C	13-12-1977
		SE 441181 B	16-09-1985
		SE 7706792 A	12-12-1977
GB 2280436 A	01-02-1995	IT 1257001 B	05-01-1996
		IT 1269339 B	26-03-1997
		AT 150594 A	15-07-1998
		AU 690138 B	23-04-1998
		AU 7532194 A	28-02-1995
		BE 1008403 A	07-05-1996
		CA 2128942 A	31-01-1995
		CH 686783 A	28-06-1996
		CN 1128020 A,B	31-07-1996
		CZ 9401831 A	15-02-1995
		DE 4426818 A	02-02-1995
		DK 89294 A	31-01-1995
		WO 9504031 A	09-02-1995
		ES 2102312 A	16-07-1997
		FI 960400 A	29-01-1996
		FR 2708601 A	10-02-1995
		GR 94100366 A	31-03-1996
		HU 9600191 A	28-11-1996
		IE 940609 A	08-02-1995
		JP 7145125 A	06-06-1995
		NL 9401229 A	16-02-1995
		NO 960376 A	29-01-1996
		NZ 271632 A	27-07-1997
		PT 101554 A	04-05-1995
		SE 9402595 A	31-01-1995
		SI 9420046 A	31-10-1996
		US 5571941 A	05-11-1996
		ZA 9405472 A	03-03-1995
DE 4425340 A	01-12-1994	NONE	
EP 108638 A	16-05-1984	AT 20733 T	15-08-1986
		DK 508283 A,B,	09-05-1984

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/02955

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 108638 A		HK 46791 A	21-06-1991
		JP 1505383 C	13-07-1989
		JP 59104352 A	16-06-1984
		JP 63055509 B	02-11-1988
		LU 88639 A	01-02-1996
		US 5349085 A	20-09-1994
-----			

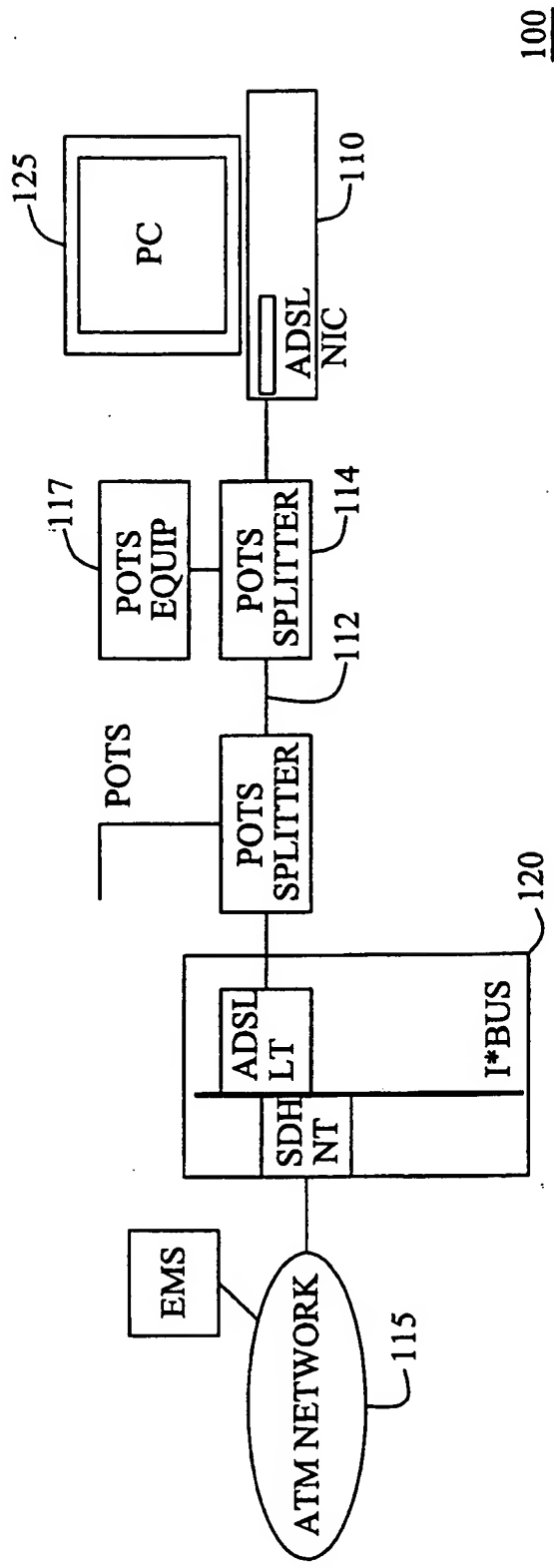


FIG 1

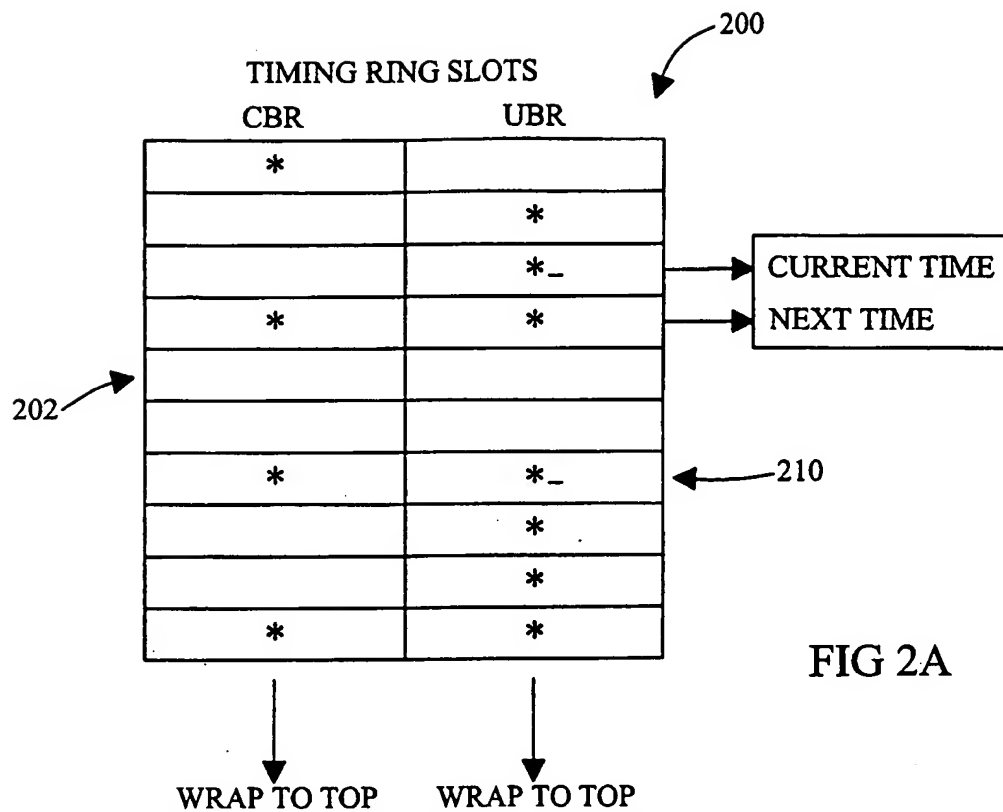


FIG 2A

\* = INDICATE THERE IS DATA TO BE TRANSMITTED.

\* \_ = INDICATE THERE IS PRIORITY UBR DATA TO BE TRANSMITTED.

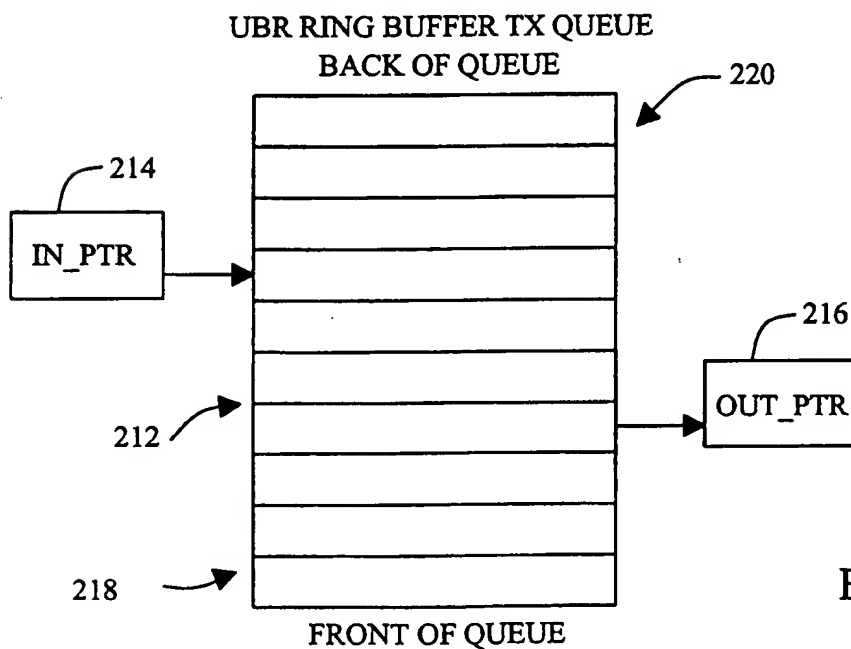


FIG 2B

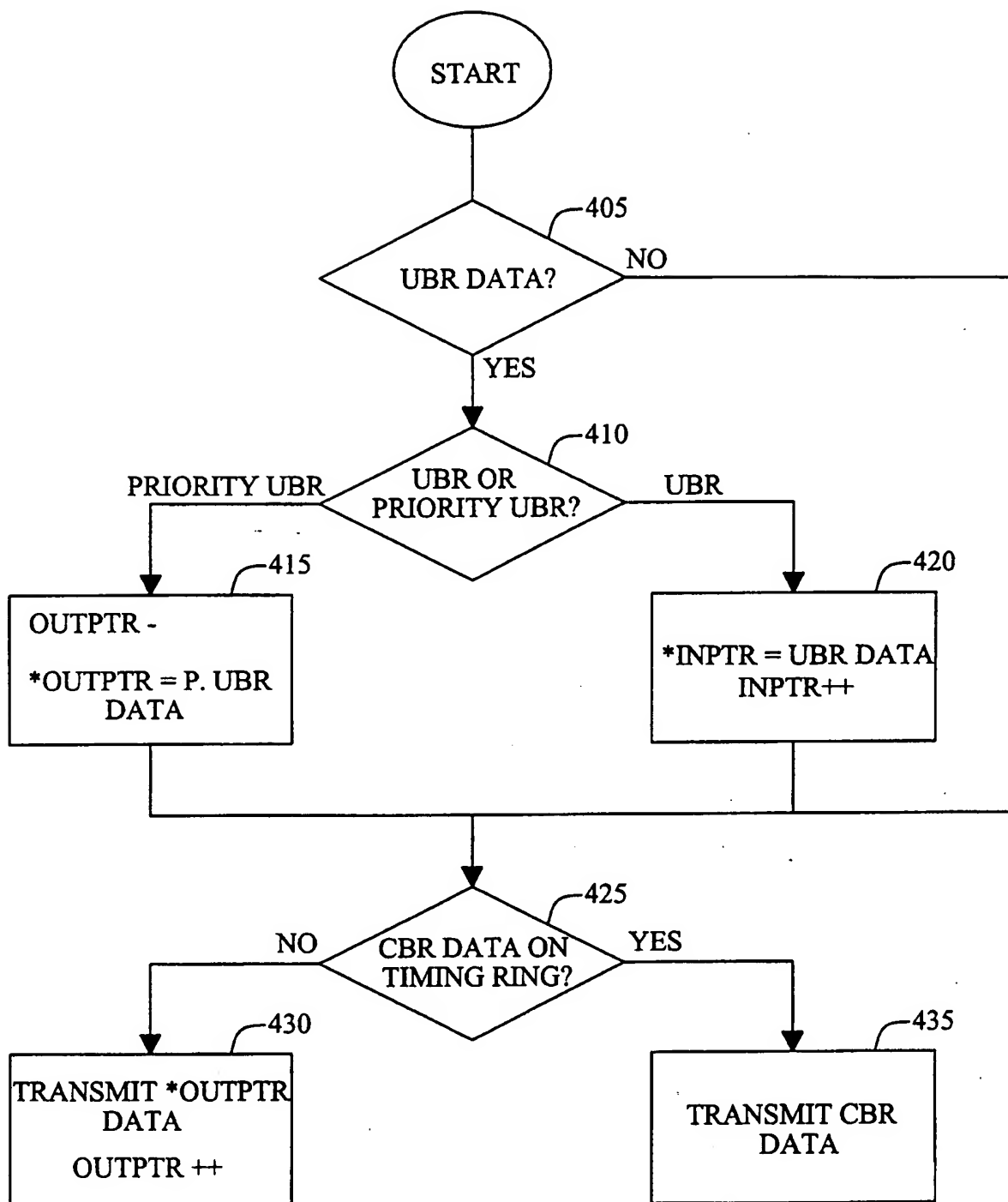


FIG 3